Br. J. clin. Pharmac. (1992), **34**, 79–81

Plasma and cerebrospinal fluid concentrations of paracetamol after a single intravenous dose of propacetamol

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Since the antipyretic and probably the analgesic effects of paracetamol are, at least in part, centrally mediated, its plasma and cerebrospinal fluid (CSF) concentrations were measured in 43 patients with nerve-root compression pain. Each subject was given a short i.v. infusion of 2 g propacetamol, a prodrug which is hydrolysed to paracetamol within 7 min. Single blood and CSF samples were drawn concomitantly in each patient at intervals between 20 min and 12 h. Maximum CSF drug concentrations were observed at the 4th hour, subsequent concentrations exceeding those in plasma. The elimination half-life of paracetamol calculated from pooled data was shorter in plasma (2.4 h) than in CSF (3.2 h). The time-course of paracetamol in CSF may parallel that of analgesic effect.

Keywords paracetamol prodrug cerebrospinal fluid pharmacokinetics

Introduction

Paracetamol is widely used for the symptomatic treatment of fever and pain. Although it is generally accepted that it acts within the preoptic hypothalamic area to produce its antipyretic effect (Insel, 1990), paracetamol is commonly considered to be a peripherally acting analgesic (Lim *et al.*, 1964). Other evidence suggests that paracetamol-induced analgesia is partly centrally mediated in animals (Carlsson & Jurna, 1987; Cheney-Thamm *et al.*, 1987; Ferrari *et al.*, 1990; Ferreira *et al.*, 1978; Hunskaar *et al.*, 1985; Tjølsen *et al.*, 1991) and in humans (Piletta *et al.*, 1991).

The biochemical mechanisms underlying the pharmacological properties of paracetamol are also unclear (Lechat & Kisch, 1989). Aspirin-like drugs reduce fever in those conditions associated with an enhanced formation of cytokines by neutrophils and other cells. Thus their antipyretic effect may be due to the inhibition of interleukin-1 induced prostaglandin (PG) E_2 synthesis from hypothalamic vascular organs (Insel, 1990). It has been suggested that the analgesic action of paracetamol is also related to the inhibition of cyclo-oxygenase (Ferreira *et al.*, 1978). However, in contrast to non steroidal anti-inflammatory drugs (NSAIDs), paracetamol has no substantial anti-inflammatory activity (Clissold, 1986). This would be explained by its weak inhibitory influence on peripheral cyclo-oxygenase (Flower & Vane, 1972), and recent clinical studies have shown that therapeutic doses do not reduce PGE_2 urinary excretion (Bippi & Frölich, 1990) or PGE_2 synovial fluid levels (Seppälä *et al.*, 1990). The hypothesis that paracetamol selectively inhibits PG synthesis in the central nervous system (CNS), may account for the discrepancies between its properties and side-effects and those of NSAIDs (Bannwarth *et al.*, 1990). Some findings are, however, inconsistent with this explanation (Bruchhausen & Baumann, 1982; Lechat & Kisch, 1989). Mechanisms which are independent of cyclo-oxygenase inhibition are likely to be involved in the antinociceptive activity of paracetamol (Tjølsen *et al.*, 1991).

In summary the available data suggest that paracetamol may act at both peripheral (Moore *et al.*, 1991) and central sites (Piletta *et al.*, 1991). In order to give support to this latter proposal, we measured plasma and cerebrospinal fluid (CSF) concentrations of paracetamol in humans after the intravenous administration of propacetamol, the hydrochloride derivative of glycine,*N*,*N*-diethyl-,4-(acetylamino)phenyl ester. Propacetamol is the sole parenteral formulation of paracetamol available in France. The vials contain 1 g powdered propacetamol, which must be dissolved in 5 ml sterile water with 0.1 g trisodium citrate just before use. Propacetamol is a prodrug, being completely hydrolysed to paracetamol by plasma esterases within 7 min after intravenous injection (Laboratories Upsa, unpublished data). With the exception of absorption,

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paracetamol exhibits similar disposition kinetics when given by either the intravenous route as propacetamol or by mouth as conventional tablets (Depré *et al.*, 1990).

Methods

Patients

Forty-three patients, 24 men and 19 women, aged 31 to 73 years (mean ± s.d.: 52 ± 12) weighing from 45 to 101 kg (72 ± 13) entered the study. All gave their written informed consent to participate in the study, which was approved by the local Ethics Committee. The patients were suffering from lumbo-sacral nerve-root compression pain that required a diagnostic lumbar puncture (myelography, cytochemical analysis of CSF). Standard laboratory tests revealed no clinically significant abnormalities in any patient.

Administration of propacetamol and sampling of biological fluids

Each patient received a single intravenous infusion of 2 g propacetamol (Pro-Dafalgan®; Upsa, Rueil Malmaison, France) over 3 min. The dosage used corresponded to 1 g paracetamol.

For ethical reasons, only one CSF sample (2 ml) was taken per patient. Peripheral venous blood (5 ml) was collected at the same time in oxalate tubes and was centrifuged to obtain plasma. Both samples were obtained between 20 min and 12 h after dosing. The CSF samples were divided in two aliquots; one was frozen with the plasma sample at −20° C until assayed, and the other was used for cytochemical analysis, which confirmed the integrity of the blood-brain barrier.

Analytical methods

Plasma and CSF samples were assayed by paracetamol by an h.p.l.c. method adapted from published procedures (Hannothiaux *et al.*, 1986; Korduba & Petruzzi, 1984; O'Connel & Zurzola, 1982). Etophylline was used as internal standard. The sample (50 µl to 0.5 ml) was extracted with 3 ml ethylacetate. The dried extract was reconstituted in 100 µl chromatographic eluent (methanol:water (25:75, v/v)) before injection onto a C_{18} column (Partisil 5 ODS-3, 5 µm, 250 × 6.35 mm, Whatman). The separation was achieved at an effluent flow-rate of 1.5 ml min^{-1}, and u.v. detection was at 245 nm. The lower limit of the assay was 2 ng ml^{-1} and the intra-assay coefficients of variation (in the concentration range of 50–1000 ng ml^{-1}) were 2.5–4.8%.

Data analysis

Individual plasma and CSF concentrations of paracetamol were pooled, and terminal elimination half-lives were estimated by log linear regression.

Results

Significant concentrations of paracetamol (0.78–2.40 µg ml^{-1}) were observed in the earliest samples of CSF taken at 20 min. Maximum CSF concentrations were observed in the 4 h samples. Thereafter the concentrations decreased to 0.26–0.88 µg ml^{-1} at 12 h. Mean as well as individual CSF paracetamol concentrations were higher than the concurrent plasma drug concentrations from the 4th to the 12th hour (Table 1 and Figure 1).

The terminal elimination half-life of paracetamol appeared to be faster in plasma (2.4 h) than in CSF (3.2 h). AUC values for plasma and CSF were similar, and were found to be about 50 µg ml^{-1} h.

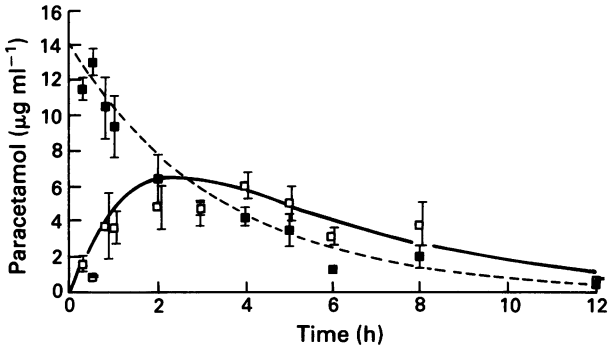

Figure 1 Plasma (■) and CSF (□) paracetamol concentrations (mean ± s.e. mean) following a single intravenous dose of propacetamol (2 g) in patients with nerve-root compression pain.

Table 1 Mean plasma and CSF concentrations of paracetamol after injection of propacetamol 2 g i.v.

Sampling time (h)	*Number of patients*	*Plasma concentration (µg ml^{-1})* mean	range	*CSF concentration (µg ml^{-1})* mean	range
0.33	3	11.46	10.88–12.03	1.54	0.78–2.40
0.50	2	13.00	12.18–13.82	0.83	0.82–0.84
0.75	4	10.50	7.53–15.20	3.68	1.36–9.04
1	5	8.18	3.94–13.60	3.58	1.75–5.83
2	4	6.37	2.54–8.97	4.75	2.13–7.12
3	4	4.38	2.91–6.14	4.68	3.65–5.26
4	4	4.19	3.04–5.36	6.00	4.81–7.64
5	4	3.45	1.55–5.87	4.97	2.88–7.66
6	5	1.27	0.85–1.74	3.13	1.92–4.44
8	3	1.96	0.95–3.16	3.79	2.31–6.22
12	5	0.33	0.23–0.44	0.61	0.26–0.88

Discussion

The estimated plasma elimination half-life of paracetamol (2.4 h) obtained from pooled data was consistent with values reported in the literature (Clissold, 1986). We have shown that paracetamol rapidly enters the CSF. This does not appear to have been demonstrated in man, although various animal studies have measured CNS concentrations of paracetamol (Cheney-Thamm *et al.*, 1987; Morgan & Freed, 1981; Ochs *et al.*, 1985). These findings are in agreement with the negligible binding of paracetamol to plasma proteins (Clissold, 1986) and the relatively high lipid solubility of the drug (*n*-octanol/phosphate buffer pH 7.4 partition coefficient = 6.2; Laboratories Upsa, unpublished data).

Our study does not allow any direct conclusion to be drawn regarding the site of action of paracetamol. It does establish, however, the presence of appreciable drug concentrations in the CSF, which could be compatible with a central action. Peak CSF drug concentrations are consistent with the delay between analgesic effect and peak plasma drug concentrations (Seymour & Rawlins, 1981). Moreover, the time-course of paracetamol in CSF may parallel that of analgesic effect (Piletta *et al.*, 1991).

The authors thank Mrs S. Leveque and C. Guillaume for their excellent technical assistance.

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(Received 29 November 1991, accepted 17 February 1992)